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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,327	01/20/2006	Hideaki Imamura	BY0018YP	2251

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EXAMINER	
BLAND, LAYLA D	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,327	IMAMURA ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9,10 and 13-18* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9, 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted May 23, 2008, wherein claims 2, 9, and 10 are amended, claims 1, 3-8, 11, and 12 are cancelled, and new claims 13-18 are added. Claims 2, 9, 10, and 13-18 are pending. Claims 13-18 are withdrawn from consideration as being drawn to a non-elected invention. Claims 2, 9, and 10 are examined on the merits herein.

In the telephonic interview of June 11, 2008, the examiner informed Mr. Muthard that language pertaining to the non-elected species could remain in the claims and that the non-elected species would be searched and examined upon allowability of the elected species. However, upon further consideration and review of the prior art, it is apparent that the elected species, a crystalline form of the free base of formula (II), would not render obvious other forms. The different forms are different products, having different molecular formulae, and the process for preparing one would be unlikely to make the other. Therefore each form must be examined separately and the search for one is not coextensive with another. Thus only the elected species, the free base of formula (II), will be searched and examined on the merits. Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant's submission of drawings on June 23, 2008 is acknowledged.

In view of the cancellation of claims 1, 3-8, 11, and 12, all rejections made with respect to those claims in the previous office action are withdrawn.

In view of Applicant's amendment submitted June 23, 2008, the rejection of claims 1, 2, and 9-12 under 35 USC 112, first paragraph is withdrawn.

The following are new rejections necessitated by Applicant's amendment submitted June 23, 2008:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 9, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 9, and 10 recite the limitations "crystalline hydrochloride salt of the compound of the formula II" and "crystalline and ethanol solvate of methanesulfonate salt of the compound of formula II." These limitations are indefinite because the chemical identity of these forms is not clearly set forth. The number of hydrochloride, methanesulfonate, and ethanol molecules with respect to the compound of formula (II) are not recited and thus it is impossible to determine the molecular formula. Furthermore, there are multiple sites within formula (II) that could form salts and it is unclear where salt formation is taking place. Seddon (Crystal Growth & Design 4(6),

1087, 2004) teaches that there should never be any doubt, in this century, about the chemical identity of a material. This new ground of rejection was necessitated by Applicant's amendment submitted June 23, 2008, wherein the limitations limitations "crystalline hydrochloride salt of the compound of the formula II" and "crystalline and ethanol solvate of methanesulfonate salt of the compound of formula II" were added to claim 2.

Claims 9 and 10 are drawn to pharmaceutical compositions or anti-tumor agents comprising the crystalline form of formula II along with pharmaceutically acceptable carriers or diluents, "wherein the crystalline form is in a solid state in the composition or agent." The phrase "wherein the crystalline form is in a solid state in the composition or agent," inserted into the claims in Applicant's amendment submitted June 23, 2008, can be interpreted in multiple ways – as a solid compound in a liquid (such as a suspension), as a solution of the compound, or as a solid compound in a solid composition. The specification, page 11, states that the pharmaceutical composition can be a liquid for injection, a freeze-dried preparation, or a powder preparation. The liquid preparation is manufactured by dissolving the compound in an appropriate solvent. The freeze-dried preparation can be prepared by dissolving the compound in a solvent and freeze-drying. The powder preparation is prepared by subdividing the crystalline compound. If Applicant intends the liquid preparation, there is a contradiction in the claim because after being dissolved, the compound would no longer be in crystalline form. This new ground of rejection was necessitated by Applicant's

amendment submitted June 23, 2008, wherein the limitation wherein the crystalline form is in a solid state in the composition or agent" was added to claims 9 and 10.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As mentioned above, the recitation "wherein the crystalline form is in a solid state in the composition or agent" is unclear and can be interpreted in multiple ways. If the limitation is interpreted to be a solid compound in a liquid (a suspension), the claims lack written description because the specification does not provide support for such compositions. This new ground of rejection was necessitated by Applicant's amendment submitted June 23, 2008, wherein the limitation wherein the crystalline form is in a solid state in the composition or agent" was added to claims 9 and 10.

Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to pharmaceutical compositions comprising a compound keeping its crystalline property, wherein the compositions include pharmaceutically

acceptable carriers or diluents. The specification, page 5, states pharmaceutically acceptable carriers and diluents include solvents and a variety of additives. The specification, page 11, states that pharmaceutical compositions can be obtained by dissolving the compound in a solvent or by freeze-drying said solution. As mentioned above, the recitation "wherein the crystalline form is in a solid state in the composition or agent" is unclear and can be interpreted in multiple ways. Claims to a solid pharmaceutical which retains the crystallinity of the compound are not enabled, as discussed below.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Muzaffar et al. (Journal of Pharmacy (Lahore) (1979), 1(1), 59-66) teach that at any one temperature and pressure only one crystal form of a drug is stable and other polymorph existing under these conditions will convert to the stable form [page 60] and that pharmaceutical preparing processes affect polymorphism [pages 63-68].

Doelker (Annales Pharmaceutiques Francaises (2002) 60(3), 161-176) teaches that one may observe changes in technological or biopharmaceutical properties that are due to polymorphic transformations arising from the mechanical or heat treatment or from environmental conditions undergone by the product or dosage form [abstract].

Doelker (S.T.P. Pharma Pratiques (1999), 9(5), 300-409) teaches that a given drug, although chemically well defined, may exhibit quite different behavior. Process conditions such as grinding, tableting, granulations, drying may affect properties of the drug such as compactibility, wettability, solubility, dissolution rate, bioavailability and pharmacological activity [abstract].

CMU Pharmaceutical polymorphism (internet pages 103 (2002)) teaches that there are a number of examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material [paragraph bridging pages 1-2].

An amorphous compound of formula (II) was prepared by Kojiri et al. (JP 10-245390, PTO-1449 submitted August 7, 2006). The compound was purified by chromatography and evaporated to dryness [0053]. Thus, the compound was dissolved in solvent, at which time no crystalline form was present, and the solvent was removed. The instant specification states that the compound prepared by this method was amorphous. Thus, the skilled artisan would expect that a crystalline compound which was dissolved in a solvent and then freeze-dried would like be amorphous as well, and would not be expected to retain the crystallinity that was lost upon going into solution.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for a crystalline form of the free base of compound (II).

However, the specification does not provide any pharmaceutical compositions that maintain the crystallinity of compound (II).

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the preponderance of evidence that crystalline compositions in pharmceutical compositions do not automatically keep their forms and the high

unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

This new ground of rejection was necessitated by Applicant's amendment submitted June 23, 2008, wherein the limitation wherein the crystalline form is in a solid state in the composition or agent" was added to claims 9 and 10.

The following rejections are maintained:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kojiri et al. (English translation of JP 10-245390, PTO-1449 submitted August 7, 2006).

Kojiri et al. teach injection of antitumor compounds, including the compound made in Example 14 [page 8, lines 5-17 and Table 1]. The compound of Example 14 [page 21, Example 14] has the same structural formula as the elected species in the instant application. Although claims 9-12 are drawn to pharmaceutical compositions or agents comprising crystalline formula (I) and Kojiri et al. do not teach a crystalline compound, the injectable composition taught by Kojiri et al. is a solution. As discussed above, the recitation "wherein the crystalline form is in a solid state in the composition or

agent" is unclear and can be interpreted in multiple ways. If the recitation is interpreted as a liquid, a solution made from a crystalline compound is the same as a solution made from the corresponding amorphous compound. Thus, the composition taught by Kojiri et al. anticipates claims 9 and 10, which can be interpreted as liquid compositions or agents for injection which can comprise solvents.

Response to Arguments

Applicant argues that the amended claims are directed to compositions and agents that comprise compounds in solid crystalline form and thus the claims are not rejected. However, the amended claim can be interpreted in multiple ways, as discussed above. If the claim is interpreted as a liquid composition prepared from using a crystalline compound, the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kojiri et al. (English translation of JP 10-245390, PTO-1449 submitted August 7, 2006).

Kojiri et al. teach compound 25, which has the same structural formula as the elected species in the instant application [page 21, Example 14]. This compound and

others prepared by Kojiri et al. can be purified by methods known in the field of organic chemistry, including recrystallization [0021].

Kojiri et al. do not teach crystalline compound 25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a crystalline form of compound 25, taught by Kojiri et al. The skilled artisan would have been motivated to do so because Kojiri et al. suggest purification by recrystallization. The skilled artisan would have had a reasonable expectation of success because recrystallization is a technique which is well known for purification of organic compounds, and could be accomplished by routine experimentation.

It is noted that the instant specification states that compounds prepared by the method of Kojiri et al. are amorphous. For this reason, claims 1 and 2 are not anticipated by Kojiri et al.

Response to Arguments

Applicant argues that the Kojiri reference does not specifically suggest recrystallization of already purified amorphous forms of the compounds and does not suggest that the compounds can be beneficially improved, other than purification, by recrystallization. Recrystallization, by definition, is expected to give a crystalline product, which is claimed. Kojiri specifically suggests that the compounds can be purified by recrystallization. Thus, Kojiri specifically suggests a process that would lead to the claimed invention. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the

basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Tuesday - Friday, 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

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Examiner, Art Unit 1623